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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,035	CHARBIT ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 January 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/05/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-14 are pending.

Drawings

2. The drawings are objected to because the text in the figures are in French and not English. Additionally, figures 7b and 7c cannot be interpreted because the images are of poor quality and are poorly labeled. All figures are difficult or impossible to interpret because they are missing legends or brief descriptions explaining the figure components and symbols. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required

corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

3. The Specification is objected to because: A reference to and brief description of the drawings as set forth in 37 CFR 1.74 is required.

Appropriate correction is required.

4. 35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms that are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: "efficient" (*see* page 1, line 4), "dispose" (*see* page 3, lines 18 and 27), "antalgic" (*see* page 4, line 9), and "posology" (*see* page 14, line 29).

Claim Rejections - 35 USC § 112 2nd Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1 and dependent Claims 2-5 and Claims 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The common use of the word "affection" is to a feeling of fondness or tenderness and not to a disease or condition. The use of the word in the claims, i.e., "an affection requiring an increase of the levels of the heme oxygenase enzyme", does not clearly define the metes and bounds of the invention that the Applicants are claiming.

7. Claims 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 9-11 are dependent claims of Claim 6 which recites the limitation "a method of **manufacturing** a medicinal product...wherein the medicinal product comprises rhein or rhein derivatives". Claims 9-11 recite methods dependent on Claim 6, of a dosage and administration of rhein or rhein derivatives. Since Claim 6 is to a method of manufacture and not a method of treatment, there is insufficient antecedent basis for these limitations in the claims.

Claim Rejections - 35 USC § 112 1st Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, those factors necessary for a *prima facie* case are discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to:

a. A method of treatment of an affliction **requiring an increase of the levels of the heme oxygenase enzyme** in a human or animal subject, comprising, administering a therapeutically effective amount of rhein or rhein derivatives, and optionally, in combination with the administration of a non-steroidal anti-inflammatory drug (NSAID) or a COX-2 inhibitor;

b. The above method, for the treatment of transplant rejection and the effects of stress on cells; and

c. A method of manufacturing a medicinal product for the of treatment of an affliction **requiring an increase of the levels of the heme oxygenase enzyme**,

comprising, manufacturing an amount of rhein or rhein derivatives, wherein the medicinal product comprises rhein or rhein derivatives.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The Applicant discloses prior art that teaches the manufacture of rhein and diacerein (*see* Specification, page 5, last paragraph to page 6, paragraphs 1-2). The prior art teaches that rhein and diacerein (diacetylrhein) have anti-inflammatory, analgesic and antipyretic activity and that they are effective in the treatment of, *inter alia*, osteoarthritis (*see* Dahms et al. "Elucidation of Phase I and Phase II Metabolic Pathways in Rhein: Species Differences and Their Potential Relevance", Drug Metabolism and Disposition, Vol 25, page 442, 1st paragraph in main body of text, and Tamura et al. "Pharmacological Studies of Diacerein in Models of Inflammation, Arthritis and Bone Resorption", European Journal of Pharmacology, Vol 448, last paragraph spanning pages 81-82). There is no prior art to indicate a nexus between rhein or rhein derivatives and heme oxygenase. The prior art teaches that diacetylrhein is completely metabolized to rhein (the presumed active agent) in humans and mammals and that diacetylrhein is not detected in plasma or liver tissue (*see* Dahms et al., page 442, 1st paragraph in main body of text). Additionally, it has been demonstrated that rhein, unlike other NSAIDs, has no effect on cyclooxygenase and does not reduce, and even seems to stimulate prostaglandin synthesis *in vivo* and *in vitro* (*see* Tamura et al., page 82, lines 12-13 and Dahms et al., lines 1-3 of 2nd paragraph in main body of text). Therefore, Tamura et al. conclude, "the mechanism of action of diacerein has not been fully clarified" (*see* page 82, lines 16-17).

(5) The relative skill of those in the art:

The relative skill is high, such as one possessing a Ph.D. or M.D. degree.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for:

a. A method of manufacturing rhein and diacerein (*supra*);

b. Demonstrating that, in an *in vitro* (cell culture) model, **diacerein** increases the expression of heme oxygenase-1 (HO-1), as evidenced in a Western blot;

c. An *in vivo* model of the effects of diacerein on tissue inflammation (i.e., cellular and host rejection reactions to implanted tissue). The Applicants' data suggests that diacerein (**statistically significant only at the highest dose, which is a very high dose relative to the dose limitations of the claims**) causes a reduction in the number of inflammatory cells, volume of cellular exudates and the formation of reactive granuloma triggered by tissue implantation. The data also suggest that diacerein, in a dose dependent manner, helped to preserve the integrity of the grafted tissue, evidenced by an increase in the collagen and glycosamino-glycan content of the grafted tissue. However, these data do not demonstrate that the effects of diacerein are mediated through HO-1. It is also noted that the data presented in figure 15 conflicts with the analogous data presented in figure 12.

However, the specification does not provide guidance for:

d. Demonstrating that rhein or diacerein increase the expression of HO-1 *in vivo*. The *in vitro* data discussed above (item b) only demonstrate theeffect of **diacerein** on HO-1 expression; however, because diacerein is completely metabolized to rhein in humans and other mammals (*supra*), *in vitro* data for diacerein fails to demonstrate the actions of rhein (the active agent) on HO-1 in a human or animal subject. Additionally, all other *in vitro* and *in vivo* data presented by the Applicants fails to demonstrate that any actions of rhein or diacerein, in humans or other animals, are mediated through HO-1.

e. Demonstrating the usefulness of co-administering NSAIDs or COX-2 inhibitors with rhein or diacerein. The data presented in figures13 and 14 fail to demonstrate any statistically significant beneficial effect of the COX-2 inhibitor, rofecoxib. Furthermore, the data presented in figure 15 actually shows a statistically significant negative effect of rofecoxib (i.e., decrease in the collagen and glycosamino-glycan content of the grafted tissue). There are no data presented for other NSAIDs.

f. Demonstrating that diacerein is effective on tissue inflammation (i.e., cellular and host rejection reactions to implanted tissue) at a dose within the dosage range of the claims, e.g., a 50 mg/kg dose (the only reported dose with statistically significant effects) would be equivalent to 3500 mg in a 70 kg human).

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regard to a lack of clarity of the mechanism of action of rhein or diacerein, and to a lack of data or prior art that teaches that HO-1 expression is increased by *in* vivo rhein or diacerein administration, the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

11. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Claim 14 depends on the method of Claim 1 for the treatment of the "effects of stress on cells and tissues". There is insufficient written description of what "stress" on cells and tissues entails.

Applicants have failed to provide any characteristics of cell or tissue stress; therefore they have not defined the metes and bounds of the claim, and have not demonstrated that they were in actual possession of the present invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 6-11 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Vittori et al. (WO 96/30034).

The instant claims are drawn to a method of manufacturing a medicinal composition comprising rhein or rhein derivatives. The intended use (i.e., the treatment of an affliction requiring an increase of the levels of heme oxygenase) confers no patentable weight to composition claims. See *In re Hack*, 114 USPQ 161

Vittori et al. teach the manufacture rhein and diacetyl rhein (diacerein) from aloin-containing substances (*see* Vittori et al., Claims 1-20) and thus clearly anticipates present Claims 6-11.

14. Claims 1-3, 5 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Tamura et al. (European Journal of Pharmacology, Vol 448) and under 35 U.S.C. 102(b) as being anticipated by Dahms et al. (Drug Metabolism and Disposition)

Both references teach that rhein and diacerein (diacetylrhein) have anti-inflammatory, analgesic and antipyretic activity and that they are effective in the treatment of, *inter alia*, osteoarthritis (*see* Dahms et al., page 442, 1st paragraph in main body of text and Tamura et al., last paragraph spanning pages 81-82). Both references

also teach the oral administration of diacerein (*see* Dahms et al.,, page 442, Abstract, line 9 and Tamura et al., page 82, line 9 of last paragraph). Additionally, Applicants disclose in instant Claim 3 that rhein and diacerein have structures as defined by formula (I) in instant Claim 2.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). **In the instant invention, the applicants must show that the teachings of the above cited references (i.e., the anti-inflammatory, analgesic, antipyretic and osteoarthritis treating properties of rhein and diacerein) do not work through the instant invention mechanism of up-regulation of heme oxygenase.** There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Therefore, Claims 1-3, 5 and 14 are anticipated by both Tamura et al. and Dahms et al. and are properly rejected.

15. Claim 12 is rejected under 35 U.S.C. 102(a) as being anticipated by Tamura et al.

In addition to the teachings of Tamura et al. previously presented (*supra*), Tamura et al. also teach the use of the NSAIDs naproxen and ibuprofen together with diacerein (*see* Abstract) as specified in instant Claim 12.

16. Claims 1-5 and 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Charbit et al. (U.S. Patent No. 6610750).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Charbit et al. teach a method of treating osteoarthritis, an inflammatory disease or condition, or an autoimmune disease, by the administration of diacerein, rhein and derivatives of rhein, at a dose of 25-500 mg/day (*see* Claims 1-5). Additionally, present Applicants disclose in instant Claim 3 that rhein and diacerein have structures as defined by formula (I) in instant Claim 2.

See the discussion in item 14 of this document that cites *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) in support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dahms et al. in view of Häyry (Abstract).

The teachings of Dahms et al. have been presented previously (*supra*).

Dahms et al. do not teach the use of rhein or diacerein in the treatment of transplant rejection.

Häyry teaches that "the etiology of chronic [allograft] rejection is most probably multifactorial" and that "the common feature in all organ allografts undergoing chronic rejections is persistent perivascular inflammation...".

One of ordinary skill has good reason to pursue the known options within his or her technical grasp, therefore it would have been obvious to try to treat organ rejection by taking advantage of the anti-inflammatory properties of diacerein.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. Claims 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al.

In addition to the teachings of Tamura et al. that have already been previously presented (*supra)*, Tamura et al. also teach suggested doses of diacerein (10-200 mg/kg/day) in their animal models (*see* page 82, Table 1). .

Tamura et al. does not teach the same dose range of diacerein as specified in the instant claim. The instant claims specify a dose of 25-500 mg/day, which is equivalent to 0.36-7.1 mg/kg/day.

It would be obvious and within the knowledge and training of one of ordinary skill in the art (someone possessing a MD or PhD degree) to determine an appropriate dose of diacerein. Such an individual would have been motivated to determine the specific dose so that they may most effectively treat the condition, based on the severity of symptoms and the response of the patient to the drug. The Applicants of the instant invention disclose on page 14 (last paragraph) that the practitioner would determine the appropriate dose according to the state of health of the patient.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 1-5 and 13-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-6 of Charbit et al. (U.S. Patent No. 6610750). Although the conflicting claims are not identical, they are not patentably distinct from each other because Charbit et al. teach a method of treating osteoarthritis, an inflammatory disease or condition, or an autoimmune disease, by the administration of rhein and diacerein, in a pharmaceutically acceptable carrier, at a dose of 25-500 mg/day. The instant claims recite a method of treating a disease or condition (including transplant rejection (an inflammatory and autoimmune condition) and other cellular and tissue "stressed" conditions) by the administration of diacerein, rhein or other rhein derivatives using a dose range of 25 to 500 mg/day. Although the instant claims do not specify the use of a pharmaceutically acceptable carrier, one of ordinary skill in the art would logically use a pharmaceutically acceptable carrier for any drug administration.

See the discussion in item 14 of this document that cites *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) in support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed.

23. Claims 1-5 and 13-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 11-13 of copending Application No. 09/768816. Although the conflicting claims are not identical, they are not patentably distinct from each other because 09/768816 teaches a method of treating inflammatory or autoimmune diseases, by the administration of rhein and diacerein, at a dose of 25-500 mg/day. The instant claims recite a method of treating a disease or condition (including transplant rejection (an inflammatory and autoimmune condition) and other cellular and tissue "stressed" conditions) by the administration of diacerein, rhein or other rhein derivatives using a dose range of 25 to 500 mg/day. Although the instant claims do not specify the use of a pharmaceutically acceptable carrier, on of ordinary skill in the art would logically use a pharmaceutically acceptable carrier for any drug administration.

See the discussion in item 14 of this document that cites *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) in support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

24. Claims 1-14 are rejected

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on Mon-Thur 8:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GP

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

7/27/07